Image AF/1634

ATTORNEY DOCKET NO. 13172.0001U1
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
	)	
Dean et al.	)	Art Unit: 1634
	)	
Application No. 09/514,113	)	Examiner: Bradley L. Sisson
	)	
Filing Date: February 28, 2000	)	Confirmation No. 9257
	)	
For: METHOD FOR REDUCING ARTIFACTS IN NUCLEIC ACID AMPLIFICATION	)	

TRANSMITTAL OF APPEAL BRIEF

MAIL STOP APPEAL BRIEF-PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NEEDLE & ROSENBERG, P.C.
Customer Number 23859

Sir:

In response to the Office Action mailed July 16, 2003, and maintained in Advisory Action mailed October 31, 2003, and pursuant to 37 C.F.R. § 1.192, enclosed is an Appeal Brief, in triplicate. A Notice of Appeal was mailed on December 16, 2003.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $165.00, representing the fee for a small entity under 37 C.F.R. § 1.17(c) and an Appeal Brief, in triplicate are enclosed.

This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

Robert A. Hodges
Registration No. 41,074

NEEDLE & ROSENBERG, P.C.
Customer Number 23859
(678) 420-9300
(678) 420-9301 (fax)

CERTIFICATE OF EXPRESS MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: MAIL STOP APPEAL BRIEF-PATENTS, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Robert A. Hodges — Date: 2/17/2004

ATTORNEY DOCKET NO. 13172.0001U1
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
	)	
Dean et al.	)	Art Unit: 1634
	)	
Application No. 09/514,113	)	Examiner: Bradley L. Sisson
	)	
Filing Date: February 28, 2000	)	Confirmation No. 9257
	)	
For: METHOD FOR REDUCING ARTIFACTS IN NUCLEIC ACID AMPLIFICATION	)	

APPEAL BRIEF

MAIL STOP APPEAL BRIEF-PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NEEDLE & ROSENBERG, P.C.
Customer Number 23859

Sir:

This is an appeal from the final rejection of claims 1-19, 21-23, 27, 31-45, and 77-80 in the Office Action mailed July 16, 2003. A Notice of Appeal was mailed on December 16, 2003.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is Molecular Staging, Inc.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to Appellants, the undersigned, or Appellants' assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-19, 21-23, 27, 31-45, and 77-80 are pending. Claims 20, 24-26, 28-30 and 46-49 have been cancelled. Claims 50-76 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1-19, 21-23, 27, 31-45, and 77-80 stand rejected. Claims 1-19, 21-23, 27, 31-45, and 77-80 are on appeal. The text of the claims on appeal are set forth in the Appendices to this Appeal Brief.

(4) STATUS OF AMENDMENTS

No amendments after final rejection have been filed.

(5) SUMMARY OF THE INVENTION

The claims on appeal are drawn to a method of reducing formation of artifacts in a nucleic acid amplification reaction, the method comprising conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer. The method of claims 1-19, 21-22 and 77-80 require that the template-deficient oligonucleotide comprises one or more template-deficient nucleotides, wherein the number and composition of template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction. Claims 23, 27, and 31-45 require that the nucleic acid amplification reaction does not involve thermal cycling.

Claims 77 and 78 require that the one or more adjacent template-deficient nucleotides are within three nucleotides of the 5' end of the template-deficient oligonucleotide. Claim 79 requires that the modified nucleotides are abasic. Claim 80 requires that the one or more

adjacent template-deficient nucleotides are within three nucleotides of the 5' end of the template-deficient oligonucleotide and that the modified nucleotides are abasic.

Template-deficient oligonucleotides and their preparation are described on page 6, line 22 through page 8, line 19 as well as page 16, lines 6-30 through page 19, line 5. Diagrams of template-deficient oligonucleotides are presented in Figures 2, 3 and 5. The method of reducing formation of artifacts in a nucleic acid amplification reaction involving using one or more of the disclosed template-deficient oligonucleotides in a nucleic acid amplification reaction is described on page 5, line 11, through page 6, line 21; page 8, line 20, through page 10, line 11; page 10, line 16, through page 11, line 5; in Figure 1; and pages 19, line 6-30 through page 20, line 21.

(6) ISSUES ON APPEAL

The issues presented on appeal are: (1) whether claims 1-19, 21-23, 27, 31-45, and 77-80 are definite as required by 35 U.S.C. § 112, second paragraph; (2) whether claims 1, 5, 8-10, 19, 22 and 77 are novel in view of Wallace (US Patent 6,027,923) under 35 U.S.C. § 102(a) and (e); and (3) whether claims 1-19, 21-23, 27, 31-45, and 77-80 are patentable subject matter as required by 35 U.S.C. §101.

(7) GROUPING OF CLAIMS

Claim 19 does not stand or fall together with claims 1, 5, 8-10, 22 and 77.

Claim 22 does not stand or fall together with claims 1, 5, 8-10, 19 and 77.

Claim 77 does not stand or fall together with claims 1, 5, 8-10, 19 and 22.

(8) ARGUMENTS

A. Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-19, 21-23, 27, 31-45, and 77-80 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellants regard as the invention. Appellants respectfully traverse this rejection.

1. The Issues

All of the rejected claims are or depend from claims 1, 23 and 77-80. The Examiner agrees that claims 1, 23 and 77-80 recite a positive process step but nevertheless contends that the claims do not recite any method steps defining how the particular template-deficient primer is to be "used" in the claim nucleic acid amplification reaction. The Examiner contends that the claims fail to define the metes and bounds of the claims.

Appellants assert that (1) present claims all include a positive process step: "conducting a nucleic acid amplification reaction", and thus are not an improper "use" claims; (2) the claims, although defining the use of the claimed template-deficient oligonucleotides broadly, adequately define the metes and bounds of the claimed method, (3) those of skill in the art would understand the metes and bounds of the claimed method.

2. The Legal Standard

35 U.S.C. § 112, second paragraph requires that: "The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which applicant regards as his invention." 35 U.S.C. § 112. The purpose of this requirement is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the

specification meets the criteria of 35 U.S.C. § 112, first paragraph, with respect to the claimed invention.

The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level skill in the pertinent art at the time the invention was made.

In reviewing a claim for compliance with 35 U.S.C. § 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. § 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent. See, e.g., Solomon v. Kimberly-Clark Corp., 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). If the language of the claim is such that a person of ordinary skill in the art can interpret the metes and bounds of the claim so as to understand how to avoid infringement, a rejection of the claim under 35 U.S.C. § 112, second paragraph, would be improper. See Morton Int'l, Inc. v. Cardinal Chem. Co., 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993). Furthermore, the breadth of a claim is not to be equated with indefiniteness. In re Miller, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated

that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. § 112, second paragraph. MPEP § 2173.04.

As discussed above, the present rejection depends on the question of whether, in view of the specification and the knowledge of those of skill in the art at the time the invention was made (as evidenced by the complete record in this application), the method of claims 1-19, 21-23, 27, 31-45 and 77-80 reasonably convey the exact subject matter encompassed within the claims. Appellants assert that the answer to this question is yes.

3. The Claimed Method Is Clear and Definite

To practice the claimed method, those of skill in the art need merely perform a nucleic acid amplification reaction using the primer specified in the claim. Although such reactions are broadly covered, this does not make the scope of the claims indefinite as it is accepted that the breadth of a claim is not to be equated with indefiniteness. In re Miller, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. § 112, second paragraph. MPEP § 2173.04.

The claims on appeal involve "a method of reducing formation of artifacts in a nucleic acid amplification reaction, the method comprising conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer..." To practice the claimed method, those of skill in the art need merely perform a nucleic acid amplification reaction using the primer specified in the claims. It is not seen how or why those of skill in the art could misinterpret the claims or be unsure of their scope. If it is a nucleic acid amplification reaction

where the specified primer is used in any way, it is covered by the claims. Appellants submit that those of skill in the art know what constitutes a nucleic acid amplification reaction and would surely know when the claimed primers are being used in such a nucleic acid amplification reaction. Armed with the Appellants' disclosure and claims along with the teachings of the prior art concerning the numerous nucleic acid amplification techniques using primers, one of skill in the art would certainly be able to interpret the metes and bounds of the claim so as to understand how to avoid infringement.

Appellants submit that those of skill in the art are well aware of the use of primers in nucleic acid amplification reactions, both what their function is and how they are to be used. Numerous nucleic acid amplification techniques using primers were devised and have been known in the art for over 30 years. Such techniques have been employed by research laboratories for at least as long. Therefore, those of skill in the art should and would know to use the template-deficient primers as they would any other primer in the chosen nucleic acid amplification reaction (and they would know and understand how to do so). Because the claims encompass numerous nucleic acid amplification reactions (which make use of primers in numerous different ways), it is understandable and entirely proper that specifics of the use of the recited primers are not in the claims. Furthermore, the law does not require that such specifics be included. For the sake of clarity, Appellants note that the knowledge and understanding of those of skill in the art is discussed above in reference to the standard for 35 U.S.C. § 112, second paragraph (i.e., that the language of the claim need only allow those of skill in the art to interpret the metes and bounds of the claim so as to understand how to avoid infringement), not in reference to enablement (though the discussion is applicable to enablement as well).

Thus, for at least the above reasons, the present claims are clear and definite and meet the requirements of 35 U.S.C. § 112, second paragraph. At least for this reason, the present rejection should be reversed.

4. The Rejection

Claims 1-19, 21-23, 27, 31-45, and 77-80 stand rejected under 35 U.S.C. § 112, second paragraph. The entire rationale of the present rejection, as set forth in the Office Action mailed July 16, 2003 (page 2), reads:

> Claims 1, 21-23, 44, 45, 77, 79, and 80 provides for the use of template deficient oligonucleotides, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps determining how this use is practiced.

The rejection fails to establish that those of skill in the art would not understand the use of the template-deficient oligonucleotides as claimed and fails to provide any rationale for why the claims are not reasonably clear, which is all the law requires. The rejection merely asserts without support that some unspecified additional detail must be recited in the claims but does not establish why or how the law requires it. Because the rejection fails to meet this burden, the rejection fails to establish a prima facie case of indefiniteness. At least for this reason, the present rejection should be reversed.

5. The Reliance on Prohibition Against "Use" Claims Is Confusing and Inapplicable

The present rejection has been based on the unpatentability of claims draw solely to the "use" of a material (see MPEP § 2173.05(q)). For example, the Office Action mailed July 16,

2003, pages 2-3, cites the rationale that claims that fail to recite any positive process steps are indefinite and cites cases holding that claims that fail to recite any positive process steps are not proper method claims and thus are not statutory subject matter. This legal principle is, however, limited to claims that completely lack any positive process step (see discussion below in connection with rejection under 35 U.S.C. § 101). Claims that include even one minimal positive process step are definite and should not be rejected as improper "use" claims. Ex parte Porter, 25 U.S.P.Q.2d 1144 (Bd. Pat. App. & Int. 1992) (holding a claim that recites the step of "utilizing" was not indefinite under 35 U.S.C. § 112, second paragraph). The prohibition against "use" claims is inapplicable to the present claims because the present claims all include a positive process step: "conducting a nucleic acid amplification reaction." The Examiner has acknowledged that the claims recite a positive process step (Advisory Action mailed October 31, 2003, page 2, lines 5-6). Accordingly, the sole legal basis for the present rejection is inapplicable to the present claims. Because the rejection fails to provide an applicable legal basis for the present rejection, the rejection fails to establish a prima facie case of indefiniteness.

The present rejection appears to be (improperly) based on a per se rule that recitation of "use" in the claims renders the claims indefinite under 35 U.S.C. § 112, second paragraph. For example, the Examiner has provided no rationale or explanation for why or how the present claims fail to reasonably set forth the metes and bounds of the claimed method. Rather, the Examiner merely states that "[a] claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced (which parallels the rationale in MPEP § 2173.05(q) for a "use" claim rejection under 35 U.S.C. § 112, second paragraph). Appellants submit that compliance with 35 U.S.C. § 112, second paragraph, is decided on the

particular facts as applied to the law, not on a per se rule. The Examiner has failed to make out a proper prima facie case for indefiniteness at least by failing to identify in what way those of skill in the art would fail to understand the metes and bounds of the claims. The facts here clearly support that the present claims are clear and definite. As discussed above, the claims do recite a positive process step and use of primers in the nucleic acid amplification reaction is clear and sufficient to provide reasonable definiteness to the claims.

For the reasons set forth above, Appellants assert that the claimed method is definite and not ambiguous. Therefore, Appellants respectfully request reversal of this rejection.

B. Rejections Under 35 U.S.C. § 102

Claims 1, 5, 8-10, 19, 22 and 77 stand rejected under 35 U.S.C. § 102(a), (e) as being anticipated by Wallace (U.S. Patent No. 6,027,923) (Wallace). Appellants respectfully traverse this rejection.

1. The Issues

Appellants submit that the present rejection depends on the proper understanding of what the prior art discloses, the proper understanding of what the current claims require, the proper understanding of the law of the novelty requirement as it applies to the claimed method, and a proper application of that law to the claimed method. Appellants note that the Examiner has failed to achieve any of these goals in the present rejection.

The Examiner contends that Wallace teaches all of the limitations of the claimed invention. The Examiner focuses on the assumption that a particular sub-region of the Wallace primers is sufficient to allow the nucleotides in this sub-region to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction.

Appellants assert that (1) the relevant region in the primers of Wallace are not alone capable of effectively priming nucleic acid synthesis in the nucleic acid amplification reaction of Wallace, (2) it is actually a major goal of Wallace to prevent the primers from effectively priming nucleic acid synthesis in the nucleic acid amplification reaction of Wallace, and (3) Wallace fails to disclose use of the primers in any nucleic acid amplification reaction where the 3' end nucleotides alone can effectively prime nucleic acid synthesis.

2. The Legal Standard

Anticipation requires strict identity: each and every element of the claimed invention must be identically set forth in a single prior art reference. See e.g., Transclean Corp v. Bridgewood Services, Inc., 290 F.3d 1364 (Fed. Cir. 2002); PIN/NIP, Inc. v. Platte Chemical Co., 304 F.3d 1235 (Fed. Cir. 2002); Sandt Technology, Ltd. v. Resco Metal and Plastics Corp., 264 F.3d 1344 (Fed. Cir. 2001); Acromed Corp v. Sofamor Danek Group, Inc., 253 F.3d 1371 (Fed. Cir. 2001).

3. The Claims On Appeal

The present claims are drawn to a method useful for reducing the formation of artifacts during nucleic acid amplification reactions that involves conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer. Use of the template-deficient oligonucleotides reduces the chance that the oligonucleotide could serve as an effective template in the formation of artifacts. The claims recite specific structures and properties for the template-deficient oligonucleotides. Specifically, claims 1 and 77 (from which the remaining claims under rejection depend) provide "...wherein the number and composition of template-capable nucleotides 3'of the template-deficient nucleotide closest to the 3'end of the template-deficient

oligonucleotide is sufficient to allow the template-capable nucleotides 3'of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction" (emphasis added). A careful reading of this claim language shows that the claims identify:

(A) a particular nucleotide in the oligonucleotide (hereinafter "nucleotide (A)", defined as "the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide"),

(B) a particular sub-region of the oligonucleotide (hereinafter "sub-region (B)", defined as the "nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide"--that is, nucleotides 3' of nucleotide (A)), and

(C) a property of this particular sub-region (hereinafter "property (C)", wherein "the number and composition of template-capable nucleotides [in sub-region (B)] is sufficient to allow the template-capable nucleotides [in sub-region (B)] alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction").

Note that property (C) is a property of sub-region (B) alone, not of the template-deficient oligonucleotide as a whole. This distinction is crucial. Further, the claim language also makes clear that property (C) is in reference to the capability of sub-region (B) "in the nucleic acid amplification reaction" (emphasis added). That is, property (C) is not a universal property of the oligonucleotide, exhibited in any and all nucleic acid amplification reactions, but rather is a property that need be present only in the particular nucleic acid amplification reaction being performed. A given oligonucleotide may meet this limitation (i.e., property (C)) in some nucleic acid amplification reactions and not others.

Submitted with this Appeal Brief is a diagram of an example of a template-deficient oligonucleotide as claimed where nucleotide (A) is highlighted in pink and sub-region (B) is highlighted in green (Appendix 3).

4. Wallace

Wallace discloses a process of amplifying a nucleic acid sequence of interest using "a unique primer, or set of primers...for each nucleic acid strand in the starting sample that contains the sequence to be amplified. The linear accumulation of primer extension products from cycle to cycle is assured through the use of primers that contain non-replicable elements – elements that halt the primer extension reaction, preventing the nucleic acid polymerase from replicating the entire sequence of the primer." Column 4, line 62, through column 5, line 2 (emphasis added). The method of Wallace involves the use of a primer with a template-deficient nucleotide, but this primer does not have the properties required of the claimed template-deficient oligonucleotides. Submitted with this Appeal Brief is a copy of Wallace Figures 1-4 where the nucleotide analogous to nucleotide (A) as described above is highlighted in pink and the sub-region analogous to sub-region (B) as described above is highlighted in green (Appendix 2). As will be seen, Wallace's analog of sub-region (B) lacks property (C) as required by the present claims. Because Wallace fails to disclose each and every feature of the present claims, Wallace fails to anticipate the present claims.

Figures 1 through 4 of Wallace show seven stages (steps (a) through (g)) of the replication of a target sequence using the method and primers disclosed by Wallace. In these figures, the original strands of the target sequence are depicted as solid lines, the primers are depicted by dashed lines, and replicated strands are depicted by dotted lines. Non-replicable

nucleotides (i.e. template-deficient nucleotides) are depicted as an "x" or an "o." In Figures 1-4, the template-deficient nucleotides appear in the middle of the primers (see Figure 1, step (b), showing the primers hybridized to the two strands of the target sequence). As the primers are extended, the template-deficient nucleotides are incorporated into the replicated strands (see Figure 1, step (c) (dashed/dotted strands)). Because the primers are incorporated into the strands, the first replicated strands are "full length" (that is, they include all of the primer sequences and primer complement sequences). As a result, the primers are fully complementary to the first replicated strands as depicted in Figure 1, step (d), where primers are shown hybridized to the two original target sequence strands (top and bottom) and the two first replicated strands (middle two strands).

When the hybridized primers of Wallace are extended on these four strands, the results differ for the original target sequence strands and the first replicated strands. As in the first round of replication, the original target sequence strands are fully replicated (see top and bottom double-stranded products in Figure 2, step (e)). However, the first replicated strands are only partially replicated (see middle two (partially) double-stranded products in Figure 2, step (e)). The partially replicated strands are marked with reference numbers 10 and 20. As can be seen, replication terminated at the template-deficient nucleotides incorporated into the first replicated strands. Thus, two of the second replicated strands (reference numbers 10 and 20) are not full length and their ends do not have a full complement of the primer sequences.

Figure 3, step (f), depicts primer hybridization (and the lack of primer hybridization) to the eight strands from Figure 2, step (e). As can be seen, the primers hybridize to, from top to bottom, the first two strands, the fourth strand, and the last three strands. The primers do not

hybridize to the third and fifth strands (and replication of those strands is, as a consequence, not primed by the primers; see Figure 4, step (g)). The third and the fifth strands are the two second replicated strands that are not full length (reference numbers 10 and 20 in Figure 2). The primers do not hybridize because these strands have insufficient sequences complementary to the primers. The strands do have some sequence complementary to the primers. Specifically (and relevantly), they have only sequence complementary to those nucleotides in the primers that are 3' of the template-deficient nucleotide. Thus, as depicted in Figure 3 of Wallace, the number and composition of template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the primers used in Wallace is not sufficient to allow the template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction of Wallace.

Note that the template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the primers of Wallace are the only nucleotides in the primer that are complementary to the second replicated strands that are not full length (reference numbers 10 and 20 in Figure 2). It is also very important to point out that a main goal of Wallace in the use of primers having template-deficient nucleotides is to prevent priming of second generation and later replicated strands by the original primers (see column 2, lines 49 - 53, where Wallace states that "...the second generation primer extension products contain at least a portion of the nucleic acid sequence of interest and cannot serve as templates for the synthesis of extension products of the primers which were extended to synthesize their templates." (emphasis added)).

5. Wallace's Primers Do Not Have The Properties of Appellants' Claims

To anticipate the present claims, Wallace must disclose every element of the claimed method. Appellants submit that Wallace does not disclose any oligonucleotide used in a nucleic acid amplification reaction where the number and composition of template-capable nucleotides 3'of the template-deficient nucleotide closest to the 3'end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3'of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction. In other words, and as shown above, Wallace fails to disclose use of any primer that has a sub-region meeting the description of sub-region (B) having property (C) as claimed.

The nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide in the primers of Wallace (the green regions in Appendix 2) are not alone capable of effectively priming nucleic acid synthesis in the nucleic acid amplification reaction of Wallace. That is, the analogous sub-region of the primers of Wallace lacks property (C). The fact that the 3' end regions of the Wallace primers lack property (C) is clearly established in Wallace. That is, the nucleotides 3' of the template deficient nucleotide are not sufficient to prime nucleic acid synthesis. This is exactly the opposite of what the present claims require. Such a deficiency in Wallace is clearly established because if the nucleotides were sufficient to prime nucleic acid synthesis, then the primers of Wallace would produce third and higher generation primer extension (which the primers do not). See, for example, Figures 3 and 4 of Wallace showing that second generation strands (labeled 10 and 20) are not replicated because the primers cannot effectively prime replication. This is because the small portion on

the second generation strands that is complementary to the primers is too short (and/or of such composition) for the primer to be able to prime replication effectively (see, for example, Wallace, col. 2, lines 49-53). This small portion corresponds to the nucleotides in the Wallace primers 3' of the template-deficient nucleotide closest to the 3' end of the Wallace primers (which makes it analogous to sub-region (B) of the claimed oligonucleotides). For this reason, the method and primers of Wallace clearly indicate that the primers of Wallace specifically lack a feature recited in the present claims.

Furthermore, preventing these higher generation of primer extension products is a major goal of Wallace. Wallace, column 9, lines 18-25, states "[t]he use of primer that contain non-replicable and/or cleavable elements ensures that, except for primer extension products synthesized on an original template nucleic acid strand present in the starting material . . .none of the synthetic nucleic acids produced during the process will serve as templates in subsequent rounds of primer extension." This is considered an advantage of the Wallace process as it is stated that "[s]till further advantages are presented as the products accumulate linearly and thus can be accurately quantified; the occurrence of "false positives" will be reduced in comparison with exponential processes that use newly-synthesized DNA as a template in subsequent rounds using the same primer." Wallace, column 13, line 6-11. Again, this is exactly the opposite of the goal of the claimed method where priming by the analogous region of the claimed template-deficient oligonucleotides is required. Because Wallace does not disclose every feature of the claimed method, Wallace cannot anticipate the claimed method.

For the reasons above, Wallace fails to anticipate claims 1, 5, 8-10, 19, 22 and 77. At least for this reason, the present rejection should be reversed.

6. The Allegation That The (B) Region Of The Template-Deficient Primer Of Wallace Is Considered To Exhibit Or Retain Property (C) Is Misguided

The Advisory Action mailed on October 31, 2003 alleges that there is no evidence of record that would refute the capability of sub-section (B) of the primers of Wallace from exhibiting property (C). The Examiner specifically alleges that the sub-region (B) of the primer of Wallace is considered to exhibit or retain property (C). In support, the Examiner cites Sommer and Tautz (Nucleic Acids Research 17(16): 6749 (1989); "Sommer") which shows that efficient priming can take place with two 3' nucleotides annealing to the template where a mismatch occurs immediately upstream and notes that the primers of Wallace have three complimentary nucleotides at the 3' terminus of the primer.

Although Sommer does suggest that successful priming can take place with three 3' nucleotides annealing to the template where a mismatch occurs immediately upstream, the primers of Sommer have complementary nucleotides other than those at the 3' end that contribute to hybrid stability of the primers (see Table I in Sommer). The present claims explicitly require that only the nucleotides 3' of the template-deficient nucleotide closest to the 3' end be considered. The present claims require that these nucleotides alone must effectively prime. Sommer does not suggest that this is possible for primers having only two or three complementary nucleotides.

Furthermore, Wallace intentionally and specifically engineered around effective priming by the 3' end nucleotides of the primer. As discussed above a main goal of Wallace in the use of primers having template-deficient nucleotides is to prevent priming of second generation and later replicated strands by the original primers (see column 2, lines 49 - 53, where Wallace states

that "...the second generation primer extension products contain at least a portion of the nucleic acid sequence of interest and cannot serve as templates for the synthesis of extension products of the primers which were extended to synthesize their templates." (emphasis added)). Such an effect is considered an advantage of the Wallace process. Wallace, column 13, line 6-11.

The present claims require that the 3' end nucleotides alone be capable of effectively priming nucleic acid synthesis "in the nucleic acid amplification reaction" (emphasis added). Thus, the claims limit the recited priming capability to the nucleic acid amplification reaction involved, not just any nucleic acid amplification. It is unquestionable that the primers of Wallace do not have the priming capability required by the present claims at least because Wallace explicitly disclaims such a capability in the nucleic acid amplification reactions disclosed in Wallace (the only nucleic acid amplification reactions taught by Wallace).

Wallace only discloses a use of primers in the specific nucleic acid amplification reaction described in Wallace (which reaction is designed to prevent efficient priming from taking place with however many complimentary nucleotides there are at the 3' terminus of the primers) and makes no disclosure as to any other use of the claimed primers in any other type of nucleic acid amplification reaction. Such a limit is evidenced by the assertion "[t]he processes of the present invention offer all the same advantages offered by other amplification reactions, plus additional benefits." Column 12, lines 65-67. The primary benefit disclosed by Wallace is, as discussed above, the inability of the second generation primer extension products to serve as templates for the synthesis of extension products of the primers which were extended to synthesize their templates. It is this process of nucleic acid amplification alone that is disclosed. Nowhere does

Wallace disclose any other process or reaction for which to use the disclosed template-deficient oligonucleotide primers.

For the reasons above, Wallace fails to anticipate claims 1, 5, 8-10, 19, 22 and 77. At least for these reasons, the present rejection should be reversed.

Claim 19 does not stand or fall together with claims 1, 5, 8-10, 22 and 77. Claim 19 involves a method of reducing the formation of artifacts in a nucleic acid amplification reaction wherein the nucleic acid amplification reaction is rolling circle amplification. Wallace fails to disclose such a limitation. For at least this additional reason, claim 19 is patentable over Wallace.

Claim 22 does not stand or fall together with claims 1, 5, 8-10, 19 and 77. Claim 22 involves a method of reducing the formation of artifacts in a nucleic acid amplification reaction, where the method comprises using a template-deficient oligonucleotide as a primer wherein the template-deficient oligonucleotide comprises one or more template-deficient nucleotides wherein all of the primers or oligonucleotides used in the nucleic acid amplification reaction are template-deficient. Wallace fails to disclose such a limitation. For at least this additional reason, claim 22 is patentable over Wallace.

Claim 77 does not stand or fall together with claims 1, 5, 8-10, 19 and 22. Claim 77 involves a method of reducing the formation of artifacts in a nucleic acid amplification reaction, where the method comprises using a template-deficient oligonucleotide as a primer wherein the template-deficient oligonucleotide comprises one or more *adjacent* template-deficient nucleotides. Wallace fails to disclose such a limitation. For at least this additional reason, claim 77 is patentable over Wallace.

For the reasons set forth above, Appellants assert that the claimed method is novel over Wallace. Therefore, Appellants respectfully request reversal of this rejection.

C. Rejection Under 35 U.S.C. § 101

Claims 1-19, 21-23, 27, 31-45, and 77-80 stand rejected under 35 U.S.C. § 101 as non-statutory subject matter. Appellants respectfully traverse this rejection.

The present rejection is based on the unpatentability of claims draw solely to the "use" of a material (see MPEP § 2173.05(q)). For example, the Office Action mailed July 16, 2003, pages 2-3, cites cases holding that claims that fail to recite any positive process steps are not proper method claims and thus are not statutory subject matter. This legal principle is, however, limited to claims that completely lack any positive process step (see discussion of cases below). Claims that include even one minimal positive process step are statutory and should not be rejected as improper "use" claims. The prohibition against "use" claims is inapplicable to the present claims because the present claims all include a positive process step: "conducting a nucleic acid amplification reaction." The Examiner has acknowledged that the claims recite a positive process step (Advisory Action mailed October 31, 2003, page 2, lines 5-6). Accordingly, the sole legal basis for the present rejection is inapplicable to the present claims. Because the rejections fails to provide an applicable legal basis for the present rejection, the rejection fails to establish a prima facie case.

The present rejection appears to be (improperly) based on per se rule that recitation of "use" in the claims renders the claims unpatentable under 35 U.S.C. § 101. For example, the Examiner has provided no rationale or explanation for why or how the present claims fail to constitute a proper process claim in light of the process step included in the claims. Rather, the

Examiner merely states that "the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101." Office Action mailed July 16, 2003, pages 2-3. This is incorrect at least because the present claims do set forth a step involved in the process ("conducting a nucleic acid amplification reaction"). This step makes the claims statutory. Reference in the claims to "using a template-deficient oligonucleotide" does not convert a statutory claim into a non-statutory claim and the Examiner has cited no authority or rationale by which this would be the case. The Examiner has failed to make out a proper prima facie case for lack of statutory subject matter at least by failing to identify how a claim that recites a positive process step could constitute non-statutory subject matter.

The rejection relies on the decisions in Ex Parte Dunki, 153 USPQ678 (Bd. App. 1967), and Clinical Products Ltd. v. Brenner, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966) (cited in MPEP § 2173.05(q)). These cases are distinguishable from the present claims. The rejection argues that Dunki and Clinical Products stand for the proposition that the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. Office Action mailed July 16, 2003, page 2-3.

The claims at issue in Dunki and Clinical Products completely lacked any positive process claim. It was this total lack of any process claim that led the Board Dunki and the court in Clinical Products to hold the claims at issue unpatentable. Specifically, the court held that the word "use" alone in the claims at issue did not describe a process, and therefore the form of the claims at issue did not come within any of the statutory classes of patentable subject matter set

forth in 35 U.S.C. § 101. Clinical Products, 255 F.Supp. at 135. In contrast, if a claim has any minimal process step, it is statutory subject matter. Because the present claims include a positive process step ("conducting a nucleic acid amplification reaction") the claims do define a process and are therefore statutory subject matter under 35 U.S.C. § 101.

For the reasons set forth above, Appellants assert that the claims constitute statutory subject matter. Therefore, Appellants respectfully request reversal of this rejection.

(9) SUMMARY AND CONCLUSION

Appellants have established that the claimed method is both definite as well as proper and statutory subject matter. In particular, Appellants have provided clear evidence that one skilled in the art, having the Appellants' disclosure and claims before him, would be possessed of a reasonable degree of certainty as to the exact subject matter encompassed within the claim. Appellants have also shown that the evidence and argument presented by the Examiner regarding the alleged indefiniteness of the claims is based on an improper legal standard.

Appellants have established that the claimed method is not anticipated by Wallace. In particular, Appellants have established that Wallace does not disclose any oligonucleotide used in a nucleic acid amplification reaction that has the structure and properties required of the claimed template-deficient oligonucleotides.

For the foregoing reasons, Appellants submit that the claims 1-19, 21-23, 27, 31-45, and 77-80 are patentable and request reversal of the rejections.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $160, representing the fee for a small entity under 37 C.F.R. § 1.17(c) is enclosed. This amount is

believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

Robert A. Hodges
Registration No. 41,074

NEEDLE & ROSENBERG, P.C.
Customer Number 23859
(678) 420-9300
(678) 420-9301 (fax)

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: MAIL STOP APPEAL BRIEF-PATENTS Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Robert A. Hodges — Date 2/17/2004

Appendix 1: Copy of Claims Involved in Appeal

1. A method of reducing formation of artifacts in a nucleic acid amplification reaction, the method comprising

conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer,

wherein the template-deficient oligonucleotide comprises one or more template-deficient nucleotides,

wherein the number and composition of template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction.

2. The method of claim 1 wherein the one or more template-deficient nucleotides are at the 5' end of the template-deficient oligonucleotide.

3. The method of claim 1 wherein the template-deficient oligonucleotide comprises two or more template-deficient nucleotides, wherein at least two of the two or more template-deficient nucleotides are adjacent.

4. The method of claim 3 wherein the two or more adjacent template-deficient nucleotides are within three nucleotides of the 5' end of the template-deficient oligonucleotide.

5. The method of claim 1 wherein the template-deficient nucleotides are selected from the group consisting of modified nucleotides, derivatized nucleotides, ribonucleotides, and nucleotide analogs.

6. The method of claim 1 wherein the template-deficient oligonucleotide comprises two or more template-deficient nucleotides, wherein at least two of the two or more template-deficient nucleotides are different.

7. The method of claim 1 wherein the template-deficient oligonucleotide comprises two or more template-deficient nucleotides, wherein at least two of the two or more template-deficient nucleotides are template-deficient for different reasons.

8. The method of claim 5 wherein the template-deficient nucleotides are modified nucleotides.

9. The method of claim 5 wherein the modified nucleotides are abasic nucleotides.

10. The method of claim 5 wherein the template-deficient nucleotides are selected from the group consisting of abasic nucleotides, nucleotides with an inverted base, fluoro substituted nucleotides, alkyl substituted nucleotides, nucleotides with phenyl substituted ethers, nucleotides with substituted thioethers, nucleotides with phosphate esters, -nucleotides, 2',3'-dideoxy nucleotides, ribonucleotides, nucleotides derivatized with biotin, nucleotides derivatized with amine, nucleotides derivatized with Hex, nucleotides derivatized with Tet, nucleotides derivatized with Fam, nucleotides derivatized with fluorescein, nucleotides derivatized with rhodamine, nucleotides derivatized with alkaline phosphatase, nucleotides derivatized with horseradish peroxidase, nucleotides derivatized with spacers, nucleotides derivatized with cholesteryl, nucleotides derivatized with DNP-TEG, nucleotides derivatized with psoralen cross-linkers, nucleotides derivatized with intercalating agents, and nucleotides derivatized with PNA conjugates.

11. The method of claim 1 wherein the nucleic acid amplification reaction does not involve cycle sequencing.

12. The method of claim 11 wherein the nucleic acid amplification reaction does not require linear amplification via thermal cycling.

13. The method of claim 12 wherein the nucleic acid amplification reaction does not involve linear amplification via thermal cycling.

14. The method of claim 1 wherein the nucleic acid amplification reaction involves exponential amplification via thermal cycling.

15. The method of claim 14 wherein the nucleic acid amplification reaction requires exponential amplification via thermal cycling.

16. The method of 14 wherein the nucleic acid amplification reaction involves the polymerase chain reaction.

17. The method of claim 1 wherein the nucleic acid amplification does not involve thermal cycling.

18. The method of 17 wherein the nucleic acid amplification is rolling circle amplification.

19. The method of claim 1 wherein the nucleic acid amplification reaction is selected from the group consisting of exponential rolling circle amplification (ERCA), rolling circle amplification (RCA), multiple displacement amplification (MDA), strand displacement amplification (SDA), nucleic acid sequence based amplification (NASBA), transcription-mediated amplification (TMA), polymerase chain reaction (PCR), self-sustained sequence replication (3SR), amplification with Q replicase, and cycle sequencing.

21. The method of claim 1 wherein all of the primers used in the nucleic acid amplification reaction are template-deficient.

22. The method of claim 1 wherein all of the oligonucleotides used in the nucleic acid amplification reaction are template-deficient.

23. A method of reducing formation of artifacts in a nucleic acid amplification reaction, the method comprising

conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer,

wherein the nucleic acid amplification reaction does not involve thermal cycling.

27. The method of 23 wherein the nucleic acid amplification is rolling circle amplification.

31. The method of claim 23 wherein the nucleic acid amplification reaction is selected from the group consisting of exponential rolling circle amplification (ERCA), rolling circle amplification (RCA), multiple displacement amplification (MDA), strand displacement amplification (SDA), nucleic acid sequence based amplification (NASBA), transcription-mediated amplification (TMA), self-sustained sequence replication (3SR), and amplification with Q replicase.

32. The method of claim 23 wherein the template-deficient oligonucleotide comprises one or more template-deficient nucleotides.

33. The method of claim 32 wherein the one or more template-deficient nucleotides are at the 5' end of the template-deficient oligonucleotide.

34. The method of claim 32 wherein the template-deficient oligonucleotide comprises two or more template-deficient nucleotides, wherein at least two of the two or more template-deficient nucleotides are adjacent.

35. The method of claim 34 wherein the two or more adjacent template-deficient nucleotides are within three nucleotides of the 5' end of the template-deficient oligonucleotide.

36. The method oligonucleotide of claim 32 wherein the template-deficient nucleotides are selected from the group consisting of modified nucleotides, derivatized nucleotides, ribonucleotides, and nucleotide analogs.

37. The method oligonucleotide of claim 32 wherein the template-deficient oligonucleotide comprises two or more template-deficient nucleotides, wherein at least two of the two or more template-deficient nucleotides are different.

38. The method of claim 32 wherein the template-deficient oligonucleotide comprises two or more template-deficient nucleotides, wherein at least two of the two or more template-deficient nucleotides are template-deficient for different reasons.

39. The method of claim 36 wherein the template-deficient nucleotides are modified nucleotides.

40. The method of claim 36 wherein the modified nucleotides are abasic nucleotides.

41. The method of claim 36 wherein the template-deficient nucleotides are selected from the group consisting of abasic nucleotides, nucleotides with an inverted base, fluoro substituted nucleotides, alkyl substituted nucleotides, nucleotides with phenyl substituted ethers, nucleotides with substituted thioethers, nucleotides with phosphate esters, (-nucleotides, 2',3'-dideoxy nucleotides, ribonucleotides, nucleotides derivatized with biotin, nucleotides derivatized with

amine, nucleotides derivatized with Hex, nucleotides derivatized with Tet, nucleotides derivatized with Fam, nucleotides derivatized with fluorescein, nucleotides derivatized with rhodamine, nucleotides derivatized with alkaline phosphatase, nucleotides derivatized with horseradish peroxidase, nucleotides derivatized with spacers, nucleotides derivatized with cholesteryl, nucleotides derivatized with DNP-TEG, nucleotides derivatized with psoralen cross-linkers, nucleotides derivatized with intercalating agents, and nucleotides derivatized with PNA conjugates.

42. The method of claim 32 wherein the number and composition of template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end is sufficient to allow the template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction.

43. The method of claim 23 wherein the template-deficient oligonucleotide is a primer.

44. The method of claim 43 wherein all of the primers used in the nucleic acid amplification reaction are template-deficient.

45. The method of claim 23 wherein all of the oligonucleotides used in the nucleic acid amplification reaction are template-deficient.

77. A method of reducing formation of artifacts in a nucleic acid amplification reaction, the method comprising

conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer,

wherein the template-deficient oligonucleotide comprises one or more template-deficient nucleotides, wherein the one or more adjacent template-deficient nucleotides are within three nucleotides of the 5' end of the template-deficient oligonucleotide,

wherein the number and composition of template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction.

78. The method of claim 77, wherein the modified nucleotides are abasic nucleotides.

79. A method of reducing formation of artifacts in a nucleic acid amplification reaction, the method comprising

conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer,

wherein the template-deficient oligonucleotide comprises one or more template-deficient nucleotides, wherein the modified nucleotides are abasic nucleotides,

wherein the number and composition of template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction.

80. A method of reducing formation of artifacts in a nucleic acid amplification reaction, the method comprising

conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer,

wherein the template-deficient oligonucleotide comprises one or more template-deficient nucleotides, wherein the one or more adjacent template-deficient nucleotides are within three nucleotides of the 5' end of the template-deficient oligonucleotide, wherein the modified nucleotides are abasic nucleotides,

wherein the number and composition of template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction.

Appendix 2

FIG. 1

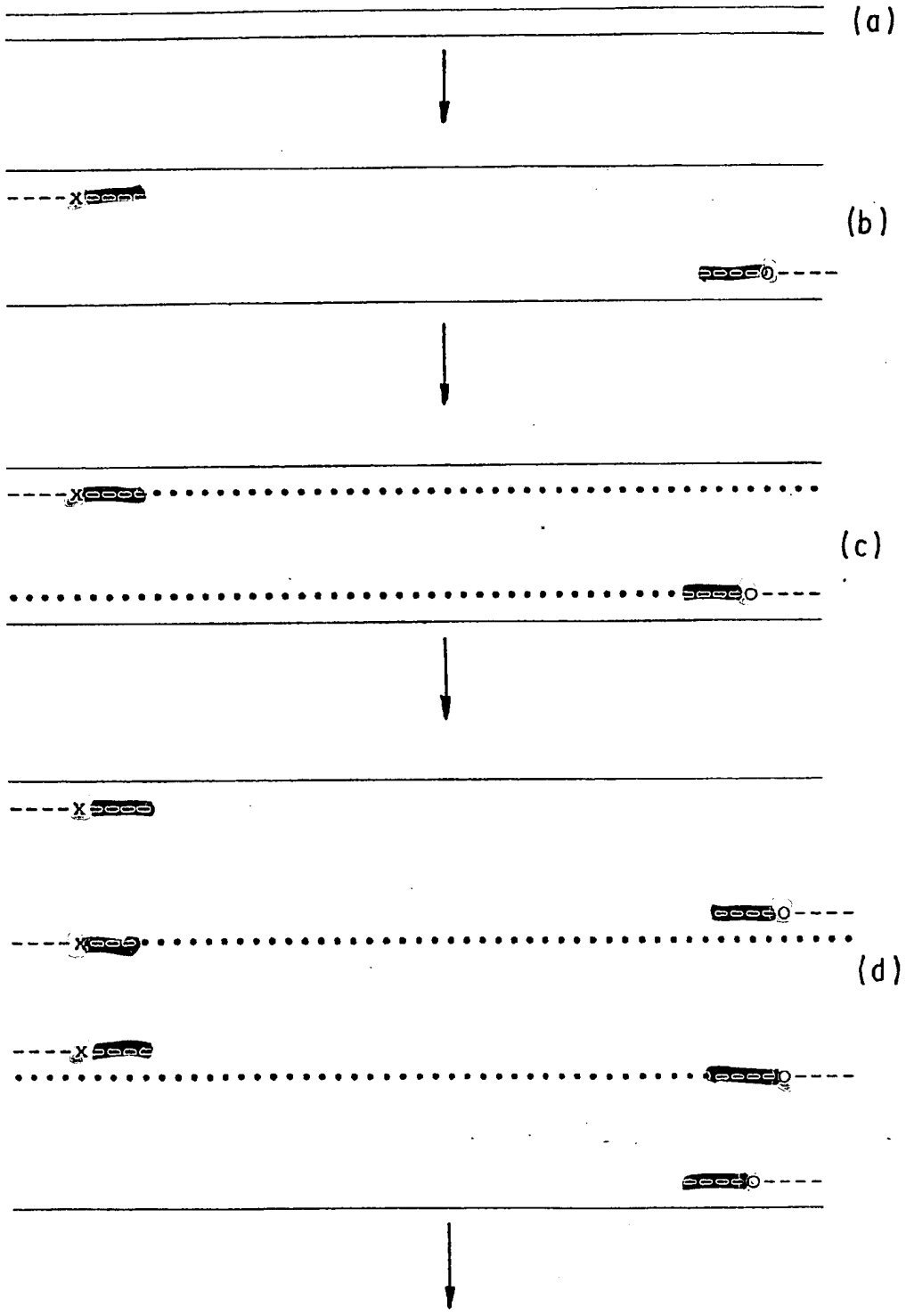


FIG.2

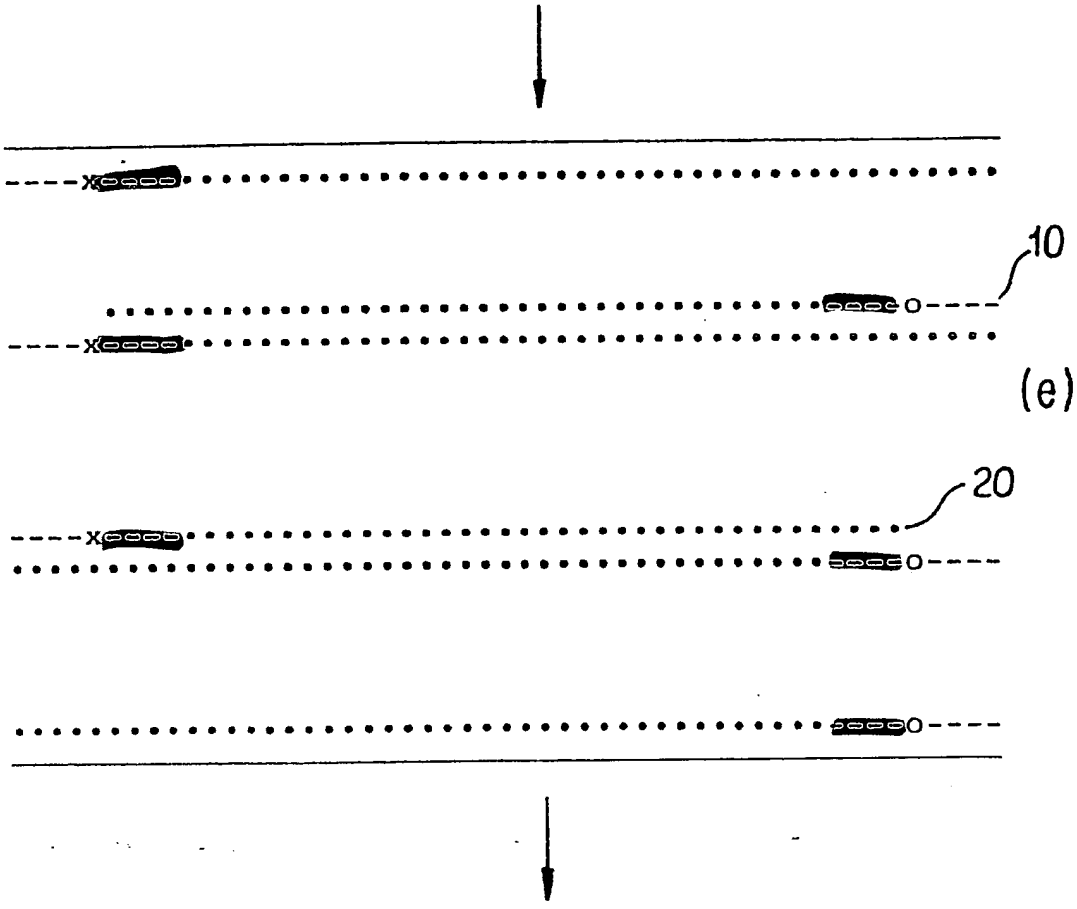


FIG.3

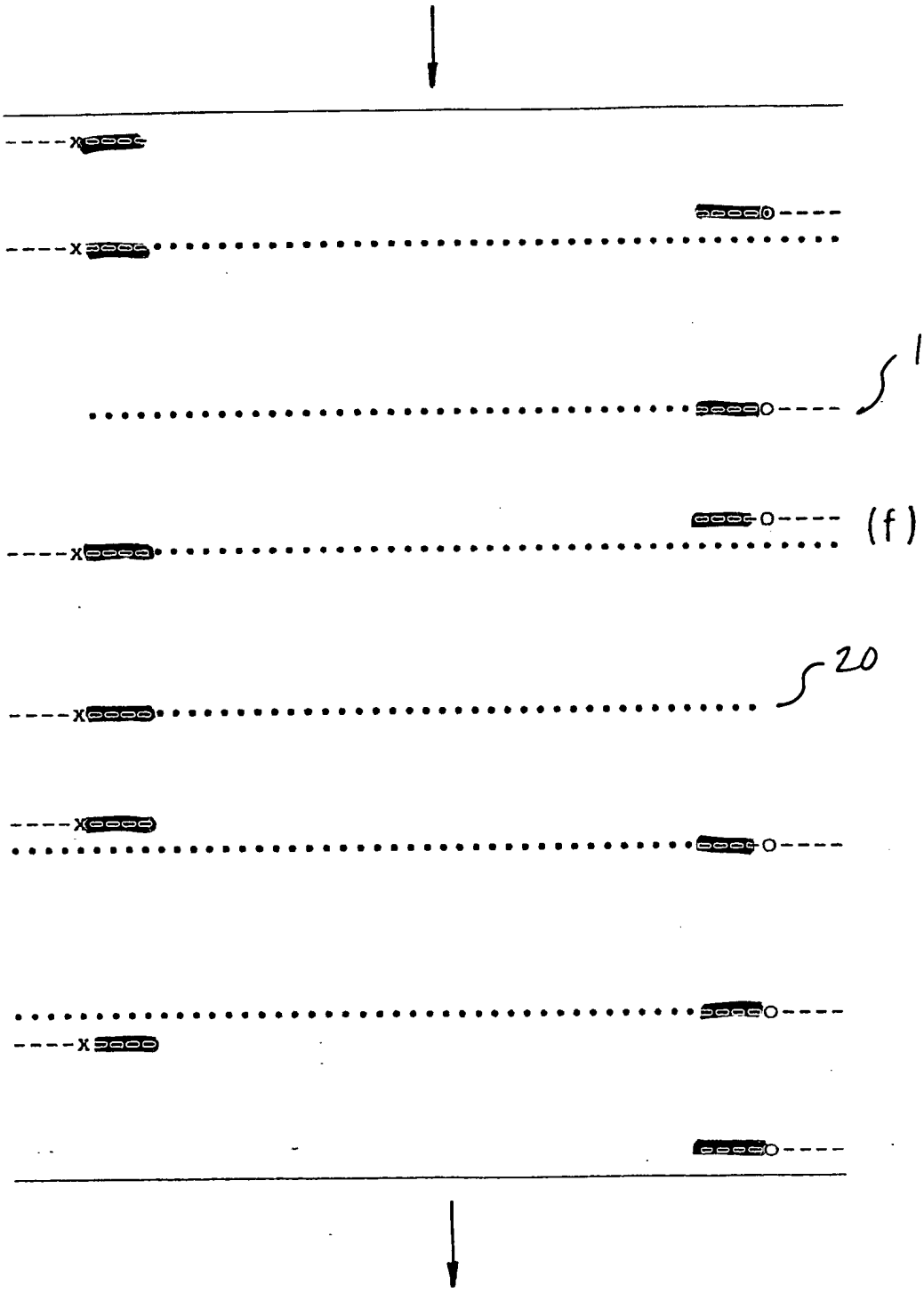
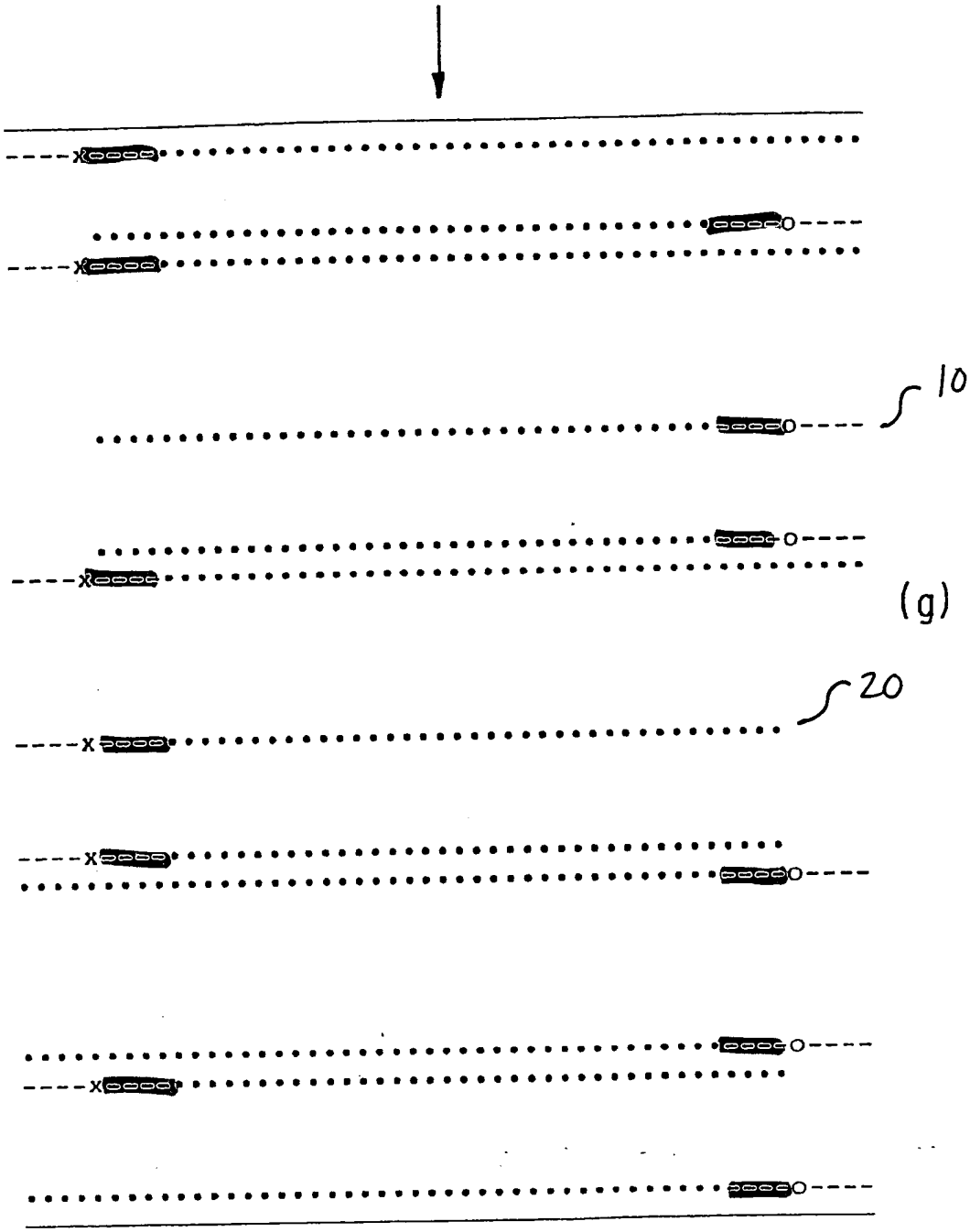


FIG.4



Appendix 3

TABLE OF CONTENTS